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10/576,496	04/20/2006	Toshihisa Komori	Q94468	4656

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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
03/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/576,496	KOMORI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009 and 21 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,15-22 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *1-4,9,15-22 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/2009; 5/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 12/21/2009 in which the specification was amended. This action is also in response to the amendment, filed 7/20/2009, in which claims 5 and 6 were amended. Claims 1-7, 9, 15-22 and 31-38 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant's election without traverse of Group II in the reply filed on 11/14/2008 is acknowledged.

Claims 1-4, 9, 15-22 and 31-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/14/2008.

Claims 5-7 are under consideration.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 3/19/2009 and 5/21/2009, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Specification

The abstract of the disclosure is objected to because it is confusing due to the amendment filed 12/21/2009. The first sentence should be rewritten to improve the grammar. The following is provided as an example: "Runx2/Cbfa1 is expressed in Runx2/Cbfa1-deficient chondrocyte cells to obtain an induced gene involved in the regulation of cartilage differentiation." Because the first sentence indicates that Runx2/Cbfa1-deficient chondrocytes are used to carry out such a method, it is not necessary to include the phrase "with a Runx2/Cbfa1-deficient chondrocyte to carry out such a method" in the second sentence of the abstract.

Correction is required. See MPEP § 608.01(b).

Response to Arguments - 35 USC § 112

Applicant's arguments, see pages 18-19, filed 7/20/2009, with respect to the rejection of claim 7 have been fully considered and are persuasive. The previous rejection of claim 7 has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al (Biochemical and Biophysical Research Communications, Vol. 273, pages 630-636, 2000, cited

in a prior action; see the entire reference). This rejection was made in the Office action mailed 2/20/2009 and has been rewritten to address the amendment to the claim in the reply filed 7/20/2009.

Claim 5 is drawn to a chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse. The present specification does not provide an explicit definition for the term "cell line"; however, the specification refers to primary cultures of chondrocytes obtained from a Runx2/Cbfa1-deficient mouse as "a Runx2/Cbfa1-deficient mouse derived primary chondrocyte cell line" (page 9, lines 11-12, which describes the cells isolated at page 62. Example 1, section (1)).

Kobayashi et al teach a Runx2/Cbfa1 deficient mouse-derived primary chondrocyte cell culture, which is a primary chondrocyte cell line (e.g., page 632, left column, 1st full paragraph; page 633, paragraph bridging columns; Figures 3B and 3D; Table 1).

Response to Arguments - 35 USC § 102

With respect to the rejection of claim 5 under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al, Applicant's arguments filed 7/20/2009 have been fully considered but they are not persuasive.

The response asserts that Kobayashi et al do not teach the presently claimed chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse. Specifically, the response asserts that Kobayashi does not teach chondrocytes which are derived from a mouse that is Runx2/Cbfa1-deficient (page 20, paragraph 3).

This argument is not found persuasive. Kobayashi et al teach the derivation of chondrocytes from a Cbfa1-deficient mouse embryos at embryonic day 18.5 (e.g., page 632, left

column, *Cell preparation and culture conditions*). Kobayashi et al specifically teach that the cells form chondrocytes in culture in the presence of rhBMP-2 (e.g., page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*). In fact, so many chondrocyte nodules formed after 12 days in culture after confluency that individual nodules were too numerous to count (e.g., Table 1). Accordingly, Kobayashi does teach chondrocytes derived from a mouse that is Runx2/Cbfa1-deficient.

At page 20, paragraph 4, the response asserts that the present cell line maintains the morphology or phenotype of a chondrocyte in spite of the deficiency of Runx2/Cbfa1. The response points to page 62, lines 4-8 and page 63, lines 2-11 of the specification for support of this statement. Furthermore, the response asserts that Enomoto et al (2004) discloses that chondrocytes isolated from Runx2-deficient mice gradually accumulate lipid droplets, show increased expression of adipocyte-related differentiation marker genes and decreased expression of type II collagen. The response asserts that Enomoto concluded that depletion of Runx2 resulted in the loss of the differentiated phenotype in chondrocytes and induced adipogenic differentiation, so that Runx2 plays an important role in maintaining the chondrocyte phenotype.

These arguments are not found persuasive. Pages 62-63 of the specification describe the analysis of the RU-1 and RU-22 cell lines, which are derived from a Runx2/Cbfa1- and p53-deficient mouse. Instant claim 5 does not require a deficiency of p53. Furthermore, Kobayashi et al recognized that chondrocytes obtained from Runc2/Cbfa1-deficient mouse have a propensity to differentiate along the adipocyte lineage (e.g., page 633, paragraph bridging columns). Thus, the later observation by Enomoto et al is not surprising. Moreover, Kobayashi et al teach that the differentiation of the cells derived from the Cbfa1-deficient mouse can be

redirected away from the adipocyte lineage and along the chondrocyte lineage by the addition of rhBMP-2 to the medium (e.g., e.g., page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*; Table 1). At page 60, Example 1, section (1), the specification describes the derivation of chondrocytes from a Runx2/Cbfa1-deficient mouse. The cells were obtained from Runx2/Cbfa1-homodeficient mice at day 18.5 of embryonic development, which is the same embryonic day used by Kobayashi et al. The specification teaches that the isolated cells were cultured for 2 or 3 days for cell proliferation and considered to have a chondrocyte morphology. Kobayashi et al teach that the cells were first cultured to confluence, and then cultured for an additional 5-25 days to observe osteoblast and adipocyte differentiation (e.g., page 632, left column, *Cell preparation and culture conditions*). At confluence very few adipocyte foci were observed (e.g., Table 1). Enomoto et al also teach the isolation of chondrocytes from embryonic day 18.5 Runx2-deficient mouse embryos (e.g., page 418, Cell culture). Enomoto et al teach that the chondrocytes actively proliferated and showed a polygonal shape until the cells reached confluence (3 days after inoculation), and on day 6 of culture some of the cells were enlarged and had accumulated many vacuoles (e.g., page 419, left column, *Runx2$^{-/-}$ chondrocytes displayed the morphology of adipocytes*). By day 9, the cells looked like adipocytes (e.g., page 419, left column, *Runx2$^{-/-}$ chondrocytes displayed the morphology of adipocytes*). The present specification, Kobayashi et al and Enomoto et al teach the same cell line derived from a Runx2/Cbfa1-deficient mouse. Applicant observed a chondrocyte morphology, because the morphology was analyzed at 2-3 days post inoculation at which time the cells have not begun to differentiate into adipocytes. Both Kobayashi et al and Enomoto et al recognized that longer term culture of the cell results in

the expression of an adipocyte phenotype. However, both Kobayashi et al and Enomoto et al teach it is within the skill of the art to control the phenotype by the addition of a factor that promotes chondrocyte differentiation. Kobayashi et al specifically teach the addition of rhBMP-2, and Enomoto et al teach that the addition of TGF-β, retinoic acid, IL-1β, PDGF, bFGF, PTH or IL-11 prevented the adipogenic changes of the Runx2$^{-/-}$ chondrocytes (e.g., page 422, paragraph bridging columns). Accordingly, Kobayashi et al teach the same primary chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse disclosed in the present specification and claimed in present claim 5.

At page 21, paragraph 1, the response asserts that Kobayashi discloses that calvarial cells are obtained from Cbfa1-deficient mice, and the cells differentiate into chondrocytes. The response asserts that the calvarial cells derived from Cbfa1-deficient mice described in Kobayashi contain numerous adipocyte foci, and the cells differentiate into chondrocytes and then into terminal hypertrophic chondrocytes. Thus, the response asserts that Kobayashi fails to obtain or disclose a homogenous cell line which stably shows phenotypes of chondrocytes.

This argument is not found persuasive. The claims are not directed to a "homogenous cell line which stably shows phenotypes of chondrocytes." As discussed above, Kobayashi et al teach the same primary chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse as disclosed at page 60 of the present specification. The present specification only examined morphology at 2-3 days post inoculation. Kobayashi et al and Enomoto et al teach that the adipocyte phenotype occurs after the cells have been cultured to confluence (more than 3 days post inoculation). Those features to which Applicant intends to rely upon to differentiate the

presently claimed invention from the teachings of Kobayashi et al are not supported by the teachings of the specification in light of the teachings of Enomoto et al.

At page 21, paragraph 2, the response asserts that based upon the disclosure of Kobayashi et al as evidenced by Enomoto et al, one of ordinary skill in the art would not have expected to obtain a homogenous chondrocyte cell line from a Runx2-deficient mouse, which maintains the phenotype of a chondrocyte in spite of the deficiency of Runx2.

This argument is not found persuasive. First, the claims do not require a homogenous chondrocyte cell line. Even so, the cells cultured prior to day 3 of Kobayashi et al would have the same degree of homogeneity as those cells disclosed in the present specification. There is no evidence to indicate that the cells are not homogenous prior to confluence. Second, Kobayashi et al teach the addition of rhBMP-2 to the medium to maintain the chondrocyte phenotype and significantly reduce the adipocyte phenotype (e.g., page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*; Table 1).

At page 21, paragraph 3, the response asserts that the present inventors were the first to succeed in establishing a chondrocyte cell line which is deficient in Runx2/Cbfa1 but surprisingly maintains the chondrocyte morphology or phenotype. The response asserts that the results are surprising and unexpected in view of the technical knowledge and understanding available in the art at the time the invention was made, as evidenced by Enomoto.

These arguments are not found persuasive. Kobayashi et al teach a primary chondrocyte cell line derived from a Runx2/Cbfa1-deficient mouse and, thus, teach each limitation of the rejected claim. Furthermore, evidence of secondary considerations, such as unexpected results,

is irrelevant to 35 U.S.C. 102 rejections and thus cannot overcome a rejection so based. *In re Wiggins*, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973). Moreover, it was not unexpected that culture conditions could be varied to promote chondrocyte differentiation of cells obtained from an embryonic day 18.5 Runx2/Cbfa1-deficient mouse. Kobayashi et al teach the addition of rhBMP-2 to the medium to maintain the chondrocyte phenotype and to significantly reduce the adipocyte phenotype (e.g., page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*; Table 1). The teachings of Enomoto et al are consistent with the teachings of Kobayashi et al and do not provide evidence of unexpected results.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al (Biochemical and Biophysical Research Communications, Vol. 273, pages 630-636, 2000, cited in a prior action; see the entire reference) in view Kamiya (Journal of Bone and Mineral Research, Vol. 17, No. 10, pages 1832-1842, October 2002, cited on the IDS filed 4/20/2006 and provided as pages 1/6-6/6; see the entire reference). This rejection was made in the Office action mailed 2/20/2009 and has been rewritten to address the amendment to the claim in the reply filed 7/20/2009.

Kobayashi et al teach a Runx2/Cbfa1 deficient mouse-derived primary chondrocyte cell line (e.g., page 633, paragraph bridging columns; Figures 3B and 3D; Table 1). The cells are derived from the anterior region of calvaria of Runx2/Cbfa1 -/- embryos at embryonic day 18.5 (E18.5) and are induced to differentiate into chondrocytes a culture comprising BMP-2 (e.g., page 632, *Cell preparation and culture conditions*; page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*).

Kobayashi et al do not teach the chondrocytes, where they are derived from a mouse that is p53 deficient in addition to being Runx2/Cbfa1-deficient.

Kamiya et al teach a p53-null mouse and the derivation of a chondrocytic cell line by clonal selection and limiting dilution from the p53-null mouse (e.g., page 2/6, 1st full paragraph; page 2/6, *Cloning of chondrocytic cells* and *Evaluation of proliferation and differentiation*; pages 3/6-4/6, *Induction of N1511 cells with either BMP/Insulin or PTH/dexamethasone*; page 4/6, *Formation of cartilage nodules and mineralization of N151*). Kamiya et al teach that the

chondrocytic cell line derived from the p53-null mouse is capable of reproducing the whole process of chondrocyte differentiation, providing an excellent model to study cartilage development, homeostasis and function (e.g., page 5/6, 2nd full paragraph). Further, Kamiya et al teach that p53-deficiency is sufficient to establish immortalized cell lines, because p53 is not present to inhibit proliferation (e.g., page 2/6, 1st full paragraph; page 5/6, 1st full paragraph; page 5/6, 2nd full paragraph; paragraph bridging pages 5/6-6/6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain a chondrocyte derived from a Runx2/Cbfa1-and p53-deficient mouse by mating the Runx2/Cbfa mouse line of Kobayashi et al with the p53 mouse line of Kamiya et al, isolating chondrocytic cells from bone at E18.5, and subjecting the cells to the cloning procedure of Kamiya et al, as well as the culture conditions to promote the differentiation of the cells to chondrocytes, because both Kobayashi et al and Kamiya et al teach obtaining cells capable of differentiating to chondrocytes in culture from a mouse deficient in a gene.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a chondrocyte cell line that is also deficient in p53, resulting in increased proliferation and immortalization in culture, while retaining the ability to differentiate to chondrocytes, as taught by Kamiya et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al in view Kamiya, Applicant's arguments filed 7/20/2009 have been fully considered but they are not persuasive.

At the paragraph bridging pages 22-23, the response asserts that the Office action has failed to establish a *prima facie* case of obviousness, because Kobayashi does not teach or suggest the presently claimed chondrocyte cell line which is deficient in Runx2/Cbfa1 but maintains the chondrocyte morphology or phenotype for the reasons set forth with regard to the rejection of claim 5.

This argument is not found persuasive for the reasons set forth above with regard to the rejection of claim 5 as being anticipated by Kobayashi et al.

At the paragraph bridging pages 22-23, the response asserts that it is admitted by the Office Action that Kobayashi does not teach or suggest chondrocytes which are derived from a mouse that is p53 deficient and Runx2/Cbfa1-deficient. Further, the response asserts that the cells described in Kobayashi contain numerous adipocyte foci, and the cells are differentiated into chondrocytes and further to terminal hypertrophic chondrocytes. Thus, the response asserts that Kobayashi fails to teach or suggest a homogenous cell line which stably shows phenotypes of chondrocytes.

These arguments are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375

(Fed. Cir. 1986). Kamiya et al teach the isolation and selection of clonal chondrocyte cell lines from p53-null mice (e.g., page 2/6, 2nd and 3rd full paragraphs). The isolation of clonal cells by limiting dilution to single cell suspensions necessarily results in homogenous cell lines. Further, Kamiya et al teach the promotion of chondrocyte differentiation in the p53-deficient cells by the addition of BMP-2 and insulin, or PTH and dexamethasone (e.g., page 2, 2nd full paragraph). Kobayashi et al teach that the addition of rhBMP-2 promotes the differentiation of the Runx2/Cbfa1-deficient cells to a chondrocyte phenotype. Thus, the combined teachings of Kobayashi et al and Kamiya et al result in the claimed chondrocyte cell line derived from a Runx2/Cbfa1- and p53-deficient mouse.

At page 23, paragraph 1, the response asserts that Kamiya does not cure the deficiency of Kobayashi, because Kamiya only teaches a specific clonal chondrocytic cell line N1511 derived from rib cartilage of a p83-null mouse. Further, the response asserts that Kamiya does not teach the claimed chondrocyte cell line derived from a mouse having both Runx2/Cbfa1- and p53-deficiency.

These arguments are not found persuasive. As discussed above, the rejection is based upon the combined teachings of Kobayashi et al and Kamiya et al. Thus, neither Kobayashi et al nor Kamiya et al alone must teach each and every limitation of the rejected claim to demonstrate a *prima facie* case of obviousness. The combined teachings of Kobayashi et al and Kamiya et al result in the claimed chondrocyte cell line of claim 6 for the reasons set forth above. Furthermore, Kamiya et al teach more than just the single N1511 cell line. Kamiya et al teach the process of isolating the clonal cell line, which one of skill in the art could readily apply to the

teachings of Kobayashi et al to obtain a clonal cell line derived from mouse deficient in Runx2/Cbfa1 and deficient in p53.

At page 23, paragraph 2, the response asserts that there would have been no expectation to obtain a stable chondrocyte cell line from a mouse which is both runx2/Cbfa1-deficient and p53-deficient even in view of Kamiya. The response asserts that, at the time the invention was made, it was thought that chondrocytes isolated from Runx2/Cbfa1-deficient mouse contained adipocytes as disclosed in Kobayashi and evidenced by Enomoto.

This argument is not found persuasive. Kobayashi et al teach how to direct the differentiation of the isolated cells away from the adipocyte lineage and towards a chondrocyte lineage by the addition of rhBMP-2 (e.g., page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*; Table 1). Kamiya et al also teach that that addition of BMP-2, in combination with insulin, directs the differentiation of p53-deficient cells towards a chondrocyte lineage (e.g., page 2/6, 3rd full paragraph). Thus, the art teaches that Runx2/Cbfa1-deficient cells and p53-deficient cells each differentiate to chondrocytes in the presence of BMP-2. One would expect that a cell line deficient in both Runx2/Cbfa1 and p53 would also be able to differentiate to a chondrocyte in the presence of BMP-2. Moreover, it would have been within the skill of the art to test the ability of a particular clonal cell line to differentiate to a chondrocyte using the methods taught by Kobayashi et al and Kamiya et al.

At the paragraph bridging pages 23-24, the response asserts that one of ordinary skill in the art would have expected that chondrocytes isolated from Runx2/Cbfa1- and p53-deficient mouse would also contain heterologous cells. Thus, the response asserts that one would not have

been motivated nor had a reasonable expectation of success in obtaining a chondrocyte cell line from Runx2/Cbfa1- and p53-deficient mouse as presently claimed.

These arguments are not found persuasive. First, the claim is not drawn to a homogenous or clonal cell line. Second, Kamiya et al the isolation of a clonal chondrocyte cell line (e.g., page 2/6, 3rd full paragraph), and it would have been within the skill of the art to apply the clonal selection process of Kamiya et al to the isolation of a chondrocyte cell line from a Runx2/Cbfa1- and p53-deficient mouse.

At page 24, paragraph 1, the response asserts that the cell taught by Kobayashi et al, as evidenced by Enomoto, cannot be used for observing chondrocyte differentiation, because the chondrocytes contain adipocytes, which are not stable and may differentiate during culture.

This argument is not found persuasive. The clonal selection procedure taught by Kamiya et al, which would be used to make the Runx2/Cbfa-deficient and p53-deficient cell line, would necessarily result in the elimination of the adipocytes. Furthermore, Kobayashi et al teach that the addition of BMP-2 inhibits adipocyte differentiation (e.g., Table 1). Thus, the cited art provides the skilled artisan with a reasonable expectation of success in overcoming any obstacles related to the presence of adipocytes in the culture. Moreover, Kamiya et al teach that the p53-deficient cell line is particularly suited for the study of chondrocyte differentiation (e.g., page 5/6, 2nd to 4th full paragraphs).

At page 24, paragraph 2, the response asserts that even if one were somehow motivated to modify Kobayashi with Kamiya in the manner asserted by the Office Action, one of ordinary skill in the art would not have obtained the presently claimed chondrocyte cell line derived from a Runx2/Cbfa1- and p53-deficient mouse for the reasons discussed above.

This argument is not found persuasive for the reasons set forth above. One would have had a reasonable expectation of success in obtaining a chondrocyte cell line derived from a Runx2/Cbfa1- and p53-deficient mouse. Furthermore, one would have been motivated to combine the teachings of Kamiya et al. to provide chondrocytes that have increased proliferation and immortalization in culture while retaining the ability to differentiate to chondrocytes, as taught by Kamiya et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636